PHARMACOLOGY

Lectures 12,13: antianginal drugs

OBJECTIVES:

- Recognize variables contributing to a balanced myocardial supply versus demand
- Differentiate between drugs used to alleviate acute anginal attacks and those meant for prophylaxis & improvement of survival
- Detail the pharmacology of nitrates and other drugs used as antianginal therapy

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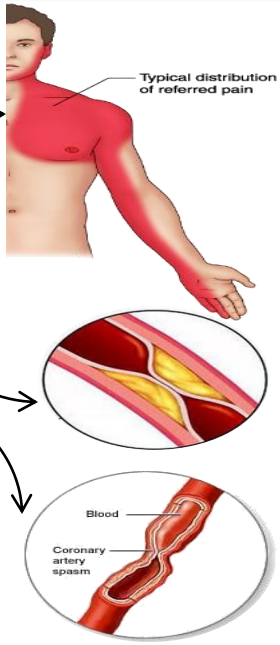
- Important.
- Extra notes.

Introduction to Angina

Which signs or symptoms suggest diagnosis of angina pectoris?

- A clinical syndrome of chest pain (varying in severity) due to ischemia of heart muscle
- Pain is caused either by obstruction (e.g. atherosclerotic plaque) or spasm
- Pain is due to accumulation of metabolites (K^+, PGs, Kinins, Adenosine….) secondary to the ischemia. These metabolites are body's response to ischemia as vasodilators.

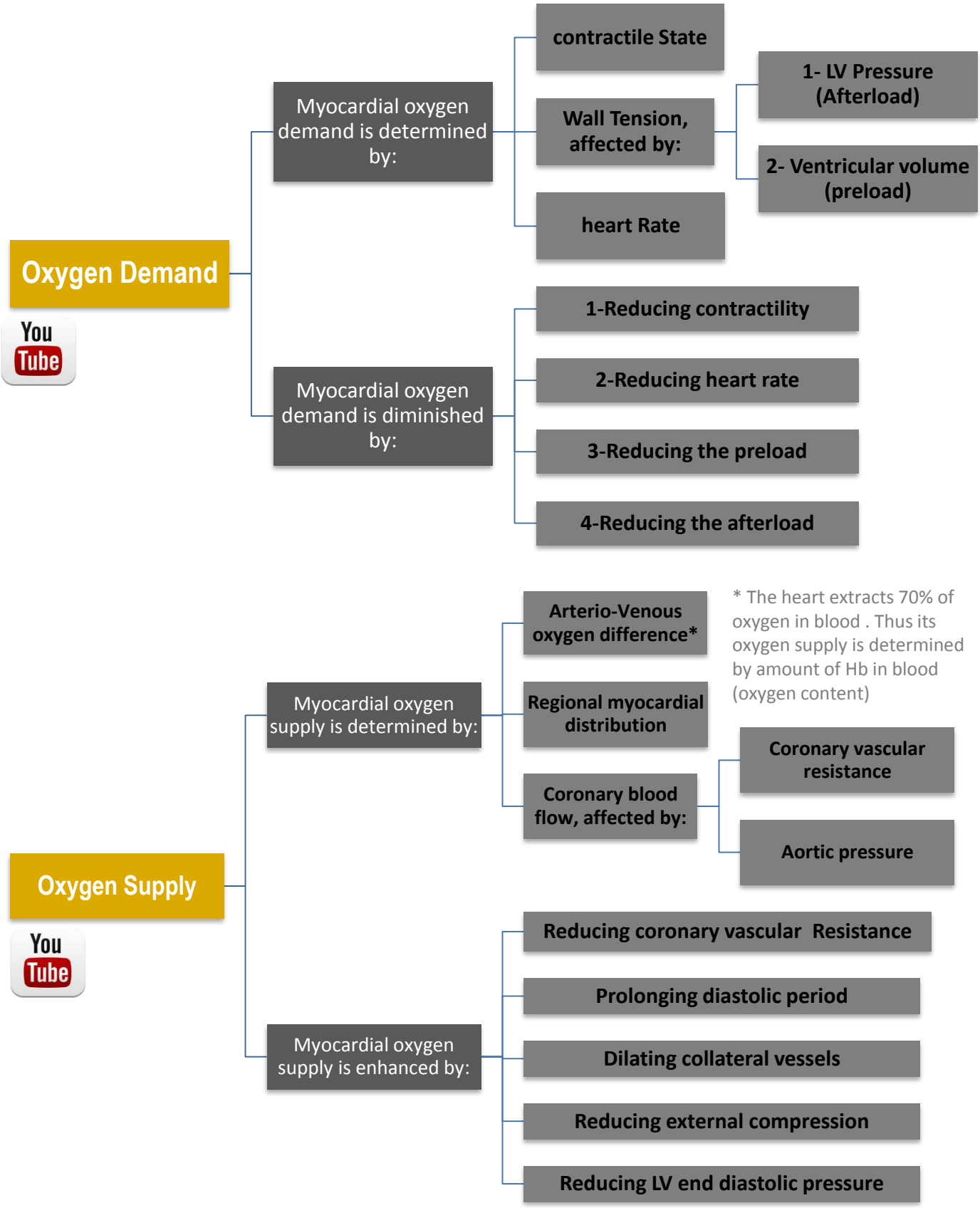


What is Basic mechanism of angina pectoris?

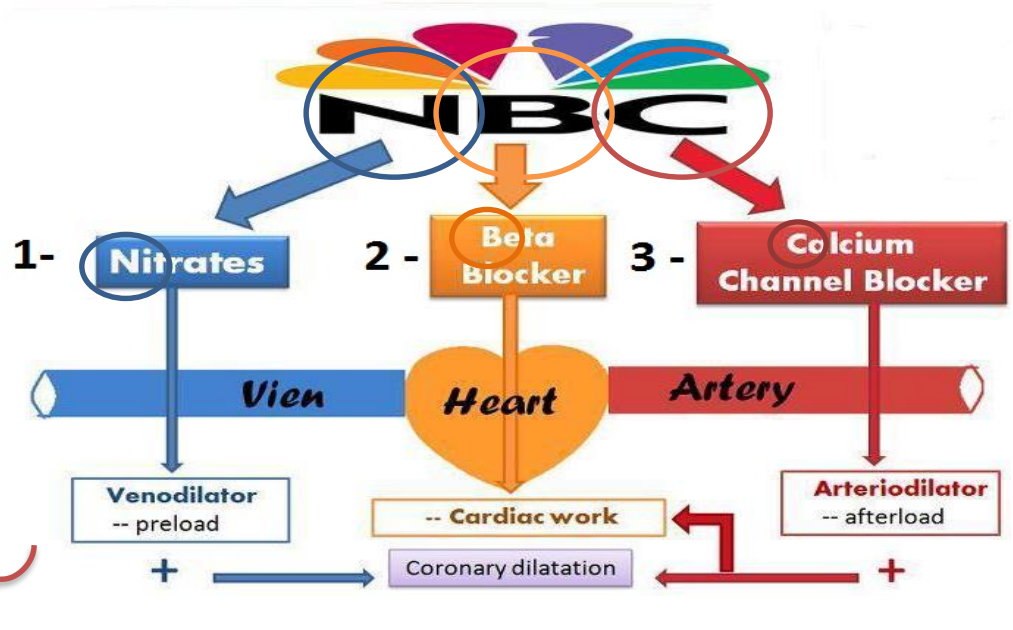
- **Angina pectoris is a consequence of <u>Myocardial oxygen demand</u> exceeding <u>myocardial oxygen supply</u>.**
- Mainly caused by obstruction of blood flow Resulting in ischemia.

Types	Stable angina	Variant angina	Unstable angina
Also known as	Effort-induced / typical / classical / chronic	Prinzmetal / vasospastic / rest angina	Accelerated angina
Cause	reduction of coronary perfusion due to a fixed obstruction of a coronary artery produced by **atherosclerosis.** The heart becomes vulnerable to ischemia whenever there is increased demand	**coronary artery spasm (Alpha receptor mediated vasoconstriction) With or without Atherosclerotic plaque.**	a form of acute coronary syndrome, caused by rupture of an atherosclerotic plaque and partial or complete thrombosis of a coronary artery.
Frequency of pain	**Pain upon exertion Exercise Emotion, Heavy meal** due to sympathetic activation (constriction)	**Pain even at rest**	**Change in pattern of chronic angina: There's increased frequency & duration of pain**
Common treatment	rest or nitroglycerin	coronary vasodilators, such as nitroglycerin and calcium channel blockers.	requires hospital admission and more aggressive therapy to prevent progression to MI and death

What are the determinants of oxygen demand and supply?



Treatment of angina pectoris



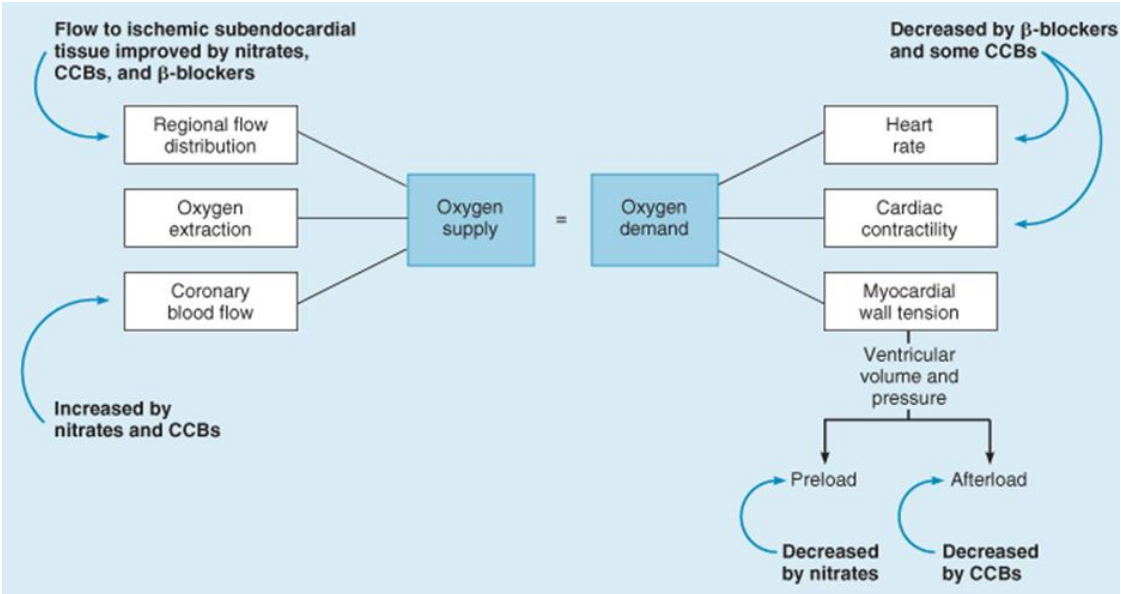
1-agents that improve symptoms & ischemia

- [ ] The drug classes mentioned in the mnemonic (NBC)
- [ ] Potassium channel openers
- [ ] Metabolically- acting agents: Trimetazidine - Ranolazine
- [ ] Ivibradine

2- agents that improve prognosis, Halt progression, Prevent acute insult

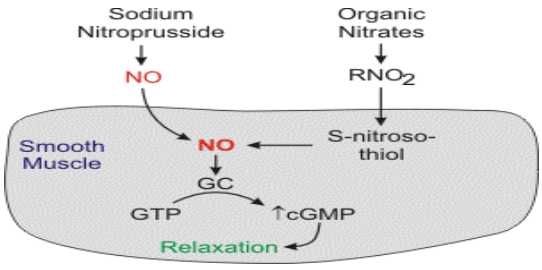
- [ ] Aspirin / other antiplatelets
- [ ] Statins
- [ ] ACE inhibitors
- [ ] β-Adrenoceptor blockers

General mechanism of antianginal drugs:



Antianginal drugs: Organic nitrates

1. Organic nitrates

Classification	Short acting	Long acting
Drugs	Nitroglycerine [GTN]	Isosorbide mononitrate & dinitrate
Pharmaco-kinetics	Can't be given orally, because it goes through Significant first pass metabolism in the liver. Only (10-20%) bioavailability	1.Very well absorbed orally (100% bioavailability). 2.The dinitrate undergoes denitration to two mononitrates ➔ both possess antianginal activity which then conjugate to glucuronic acid in liver. 3. T1/2= 1-3 hours 4.Excreted in urine.
Main Use	Rapid For terminating an **acute attack of stable angina**	For long-term **Persistent prophylaxis of stable angina.**
Preparations & indications	▪**Sublingual tablets** or spray: Have rapid onset of action and short duration (30min), thus used for: • **Acute symptom relief & Situational prophylaxis "as in before exercise" in stable angina** • **Also used for variant angina** ▪ Transdermal patch (8-14h). ▪ Oral or bucal sustained release (4-8h) ▪ **I.V. Preparations (used for unstable angina, acute heart failure, & MI).**	▪Dinitrate Sublingual tablets ▪Dinitrate Oral sustained release ▪Mononitrate Oral sustained release ▪Infusion Preparations ▪In **chronic heart failure Isosorbide mononitrate + hydralazine as 2nd line treatment. (1st line treatment are ACE inhibitors)**
Mechanism	1- release nitric oxides through enzymatic reaction by nitrosothiols. **Nitric oxide then** binds to guanylate cyclase in vascular smooth muscle cell to form cGMP. 2- **cGMP** activates PKG (*Protein Kinase G)* to produce relaxation note: For the action of Nitrates we need sulfur.	
Hemodynamic effects of nitrates	Nitrates can treat angina pectoris by one of 4 mechanism: 1- Decrease the preload pool the blood inside veins ➔ reduce the amount of blood inside the LV ➔ decreases the Venous Return ➔ decrease O2 demand 2- Increase the myocardial perfusion (O2 supply) by dilating the coronary vessels. 3- Arterial vasodilatation ➔ ↓ Afterload. although their main effect is dialation of veins (reducing preload), they can affect arteries in high doses (reducing afterload) 4- Shunting of flow from normal area to ischemic area by dilating collateral vessels. **(blood in ischemic area increases).**	

Antianginal drugs: Organic nitrates (cont.)

NIRATE TOLERANCE	➢ **WHEN ? Loss of vasodilator response of nitrates on use of long-acting preparations (oral, transdermal) or continuous intravenous infusions, for more than a few hours without interruption.** ➢ **How?, mechanism:** 1. **Compensatory neurohormonal counter-regulation** and sympathetic activation. 2. **Depletion of free-SH groups.** note: For the action of Nitrates we need sulfur. ➢ **How to overcome tolerance? by: free periods (Smaller doses at increasing intervals) & Giving drugs that maintain tissue SH group e.g. Captopril.**
ADRs	• Postural hypotension with reflex tachycardia. Leading to increasing oxygen demand. • Nitrite syncope with fainting & dizziness (treated by low head position) • Flushing of blush area (due to dilation of cutaneous blood vessels). • Throbbing headache (>common), due to dilation of cranial blood vessels. • Met-hemoglobinemia (rarely, in overdose & accidental poisoning)
Contra-indications	• Known **sensitivity** to organic nitrates • Glaucoma. nitrates increase synthesis of aqueous humor and thus increase intraocular pressure. • **Head trauma or cerebral haemorrhage** ➔ Increase intracranial pressure . لان الدماغ محجوز بالجمجمه فلو صار فيه توسع في الشرايين هذا بيضغط على الانسجه وبيزيد الضغط معه • Uncorrected hypovolemia, because reduction of volume in the body will result in vasoconstriction. Hypovolemia must be corrected before administration of nitrates. • Concomitant administration of PDE5 Inhibitors. Because they act synergistically and cause severe hypotension.

Organic nitrates (very important notes):

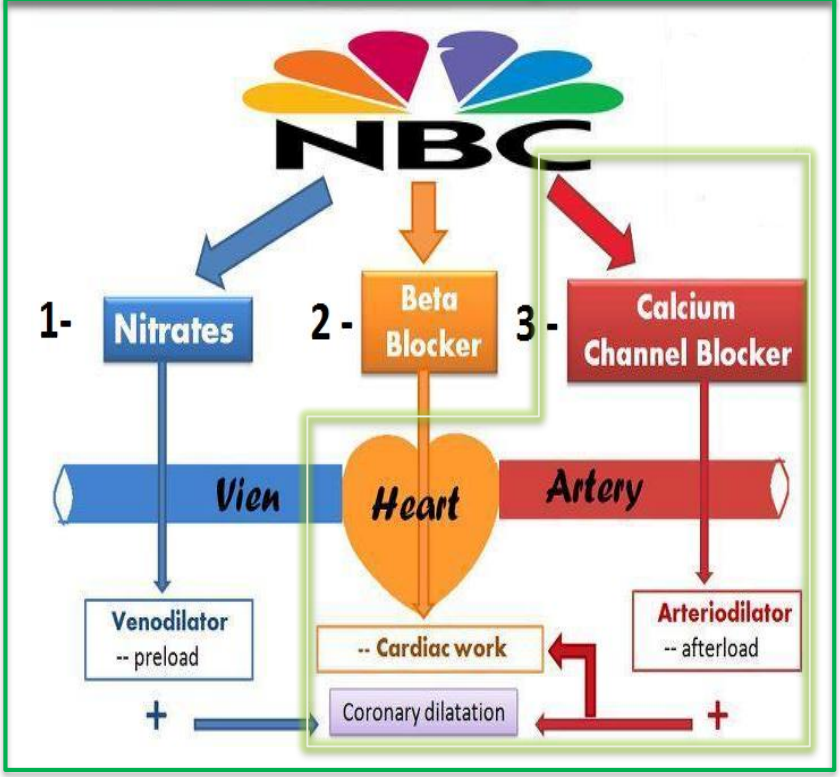
1-↓Arterial pressure is causing ↓ O2 demand …
how? **When the BP is high the heart must contract forcfuly to pump blood inside the arteries and this increas the work load, but here the dreacreas in the arterial prsuure will lead to** decreasing the afterload **and as a result decrease in O2 demand.**
*(نلاحظ أن هذه الفقرة مناقضة للرفليكس ؟؟ لأنه شخص من الأساس عنده انخفاض في الضغط)
2-Reflex ↑ in contractility is causing ↑ O2 demand…
how ? A **high dose** nitrate will dilate **arteries** and this helps in decreasing the afterload with a fall in BP that stimulates the sympathetic activities resulting in **reflex tachycardia + increase contractility.** both will increase O2 demand.
3-↑Collateral flow is causing Improved perfusion to ischemic myocardium.
4-↓Ventricular volume is causing ↓ O2 demand … how ? Decreasing the Ventricular volume means we are decreasing the **preload** which lead to ↓ O2 demand.
5- Reflex tachycardia is causing ↑ O2 demand ... As explained earlier.
6-↓Left ventricular diastolic pressure is causing Improve subendocardial perfusion.
7-↓Diastolic perfusion time due to tachycardia is causing ↓ myocardial perfusion.
8- Vasodilation of epicardial coronary arteries is causing Relief of coronary artery spasm.

Calcium channel blockers (CCBs)

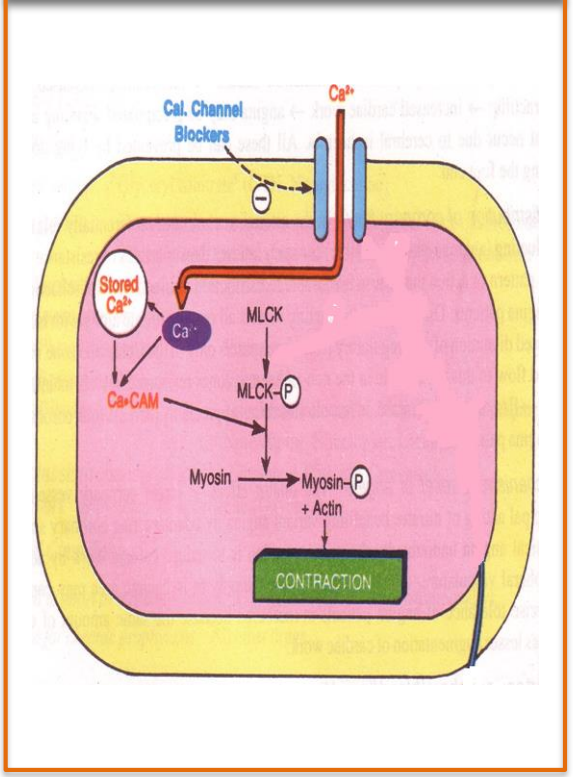
2. CALCIUM CHANNEL BLOCKERS (CCBS)

Drugs	**Classifications:**	**Selectivity:**
	Dihydropyridines: **Nifedipine , Nicardipine** ***(short acting)*** **Amlodepine** ***(long acting)***	Selective for VSMCs more than myocytes (VSMCs= vascular smooth muscle cells)
	Phenylalkylamines **e.g. Verapamil**	Cardiomyocytes more than VSMCs
	Benzthiazepines e.g. **Diltiazem**	Intermediate action on both
Mechanism	Calcium channel blockers ➔ Bind to L Type Ca channels ➔ decrease their frequency of opening in response to depolarization ➔ ↓entry of Ca ➔ ↓ Ca release from internal stores ➔ No Stimulus-Contraction Coupling ➔ **RELAXATION**	
Pharmaco-dynamic Antianginal actions	**↓ Cardiomyocyte Contraction** (verapamil & diltiazem)	**↓VSMC Contraction** ➔ arteriolar vasodilation (as Dihydropyridines)
	↓cardiac work through their –ve inotropic & chronotropic action ➔ **↓myocardial oxygen demand**	1-↓ After load ➔ ↓cardiac work ➔ **↓myocardial oxygen demand** 2-coronarydilatation **↑myocardial oxygen supply**
Indications	➢ IN VARIANT ANGINA: Attacks are prevented by dilation of coronary vessels. ➢ IN UNSTABLE ANGINA: Seldom (rarely) added in refractory cases ➢ IN STABLE ANGINA: Regular prophylaxis	

Pharmaco-dynamic Antianginal actions



Mechanism



Calcium channel blockers (cont.) , K channel openers

2. CALCIUM CHANNEL BLOCKER (cont.)

Short acting dihydropyridine (Nifedipine , Nicardipine) should be AVOIDED?

Yes, because it is short acting calcium channel blocker that works on blood vessels , which means that it will lead to vasodilation ➔ hypotension and syncope ➔ the sympathetic will be activated ➔reflex tachycardia ➔ less diastolic duration ➔ impair coronary filling ➔ ischemia or myocardial infraction

Is calcium channel blocker useful antianginal in patients with CHF (Congestive heart failure)?

Yes, dihydropyrdine: to reduce the afterload and thus decreasing the cardiac workload.

Can we combine Calcium Channel Blocker with beta blocker?

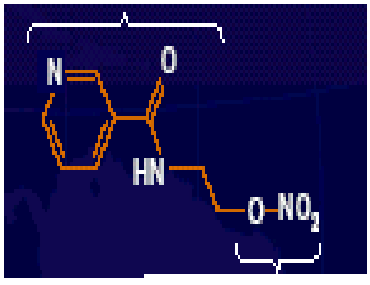
Yes, dihydropyrdine: because beta blocker works on the heart so we can not combine it with CCB that also work on the heart (cardiomyocyte). but we can give something works on the blood vessel like the long acting dihydropyrdnes: amlodepine

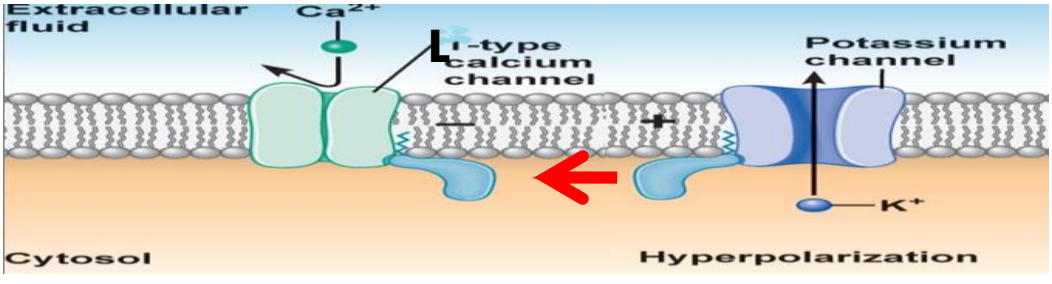
Can we combine Calcium Channel blocker with Nitrate ?

Yes, Verapamil: Because Nitrate is a vasodilator, that causes hypotension which leads to reflex tachycardia (increasing in the heart rate) and increasing in the force of contraction, so we can combine it with a CCB that works on the heart (cardiomyocyte) like verapamil to reduce the heart rate and the contraction.

3. K^+ CHANNEL **OPENERS**

Drug	Nicorandil	
Pharmaco-dynamic (dual mechanism)	**1.Opening of K_{ATP} channels**	**2. Acting as NO donner**
	On VSMCs :K^+ channel opening ➔ Hyperpolarization **with shutting off the calcium channel leading to relaxation ➔ VASODILATATION (improve coronary flow & ↓afterload)**	On VSMCs : NO donner➔ ↑ cGMP/ PKG ➔ **VASODILATATION**
	On Cardiomyocyte : K channel opening➔ Repolarization ➔ relaxation of myocardial cells ➔ **↓Cardiac work**	
Indications	1. Prophylactic 2nd line therapy in stable angina 2. Refractory variant angina if not responding to nitrate and CCB	
ADRs	Flushing, headache, Hypotension, palpitation (due to nitrate effect) Weakness, **Mouth & peri-anal ulcers**, nausea and vomiting	





β Adrenergic Blockers

4. β Adrenergic Blockers

β Blockers	Type	**Selective β1 blocker**
	Examples	Atenolol, Bisoprolol, Metoprolol
	Site	cardiomyocyte
Pharmaco-dynamic	1- Negative inotropic effect (↓ force of contraction) 2- Negative chronotropic effect (↓Heart rate = bradycardia)	
	3- ↓cardiac work	3- Increase diastolic duration Due to the bradycardia 4- Increase coronary blood flow
	4- ↓myocardial oxygen demand	**5- ↑ myocardial oxygen supply.**
1-Indication as antianginal	Stable	1- Cardio-selective (beta 1 blockers) are preferred 2- prolonged use reduce incidence of sudden death by preventing ventricular tachycardia due to their antiarrhythmic action.
	Variant	**Contraindicated**, because they are ineffective and may actually worsen symptoms.
	Unstable	**halts progression to AMI → improve survival**
2- in acute Myocardial infraction	Given early to ↓Infarct size, morbidity & mortality (↓ incidence of sudden death)	

Are Cardioselective beta blocker s preferred in angina?

Yes, beta 1 blockers are preferred, and non selective beta blockers are better avoided as they block vasodilatory effects of sympathetic stimulation that tend to increase afterload & O2 consumption.

Prolong use of beta blocker reduces incidence of sudden death?

Yes, They are 1st choice on prolonged use to reduce incidence of sudden death specially due to preventing ventricular tachycardia by their antiarrhythmic action the Negative chronotropic effect

Does Beta blocker should be withdrawn gradually?

Yes, Because sudden stoppage will give rise to a withdrawal syndrome: Increase pain, Rebound angina, arrhythmia, myocardial infarction & Hypertension (due to stimulation or Up-regulation of beta-receptors).

Can we give a beta blocker to diabetic patient with ischemic heart disease?

We can give it CAUSIOUSLY بحذر if benefits are more than risks

They cause hypoglycemia (increase insulin and reduce glycogenolysis) and mask its symptoms, they also inhibit the counter-regulatory mechanism and thus prevent recovery of hypoglycemia.

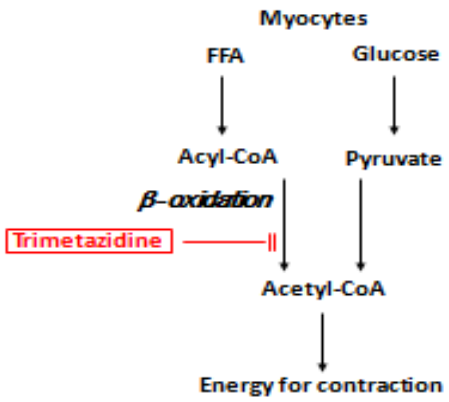
بالتالي نقيس فائدتها عالمريض، إذا ضررها أكثر من نفعها فالأفضل طبعًا عدم إعطاءه.

Metabolically Acting Agents

5. Metabolically Acting Agents

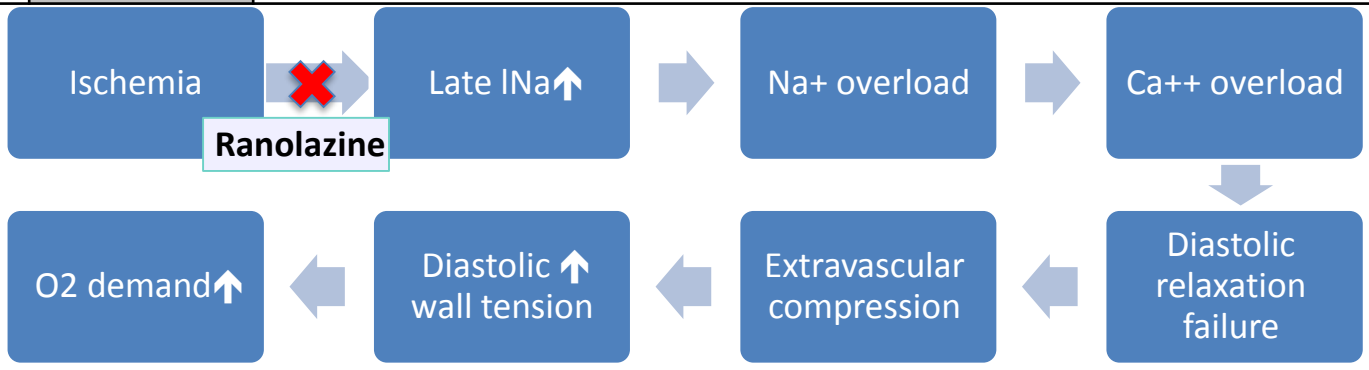
1. Trimetazidine

Pharmacological effect	During ischemia, metabolism shifts to oxidation of FFA (fatty acids), which provides more energy but requires more O2 than Glucose utilization. So, to decrease O2 consumption & demand, we can enhance utilization of glucose (less O2 requirement) by giving Partial FFA Oxidation Inhibitors (e.g. Trimetazidine) Resulting in increasing the metabolic rate of glucose, thus decreases O2 consumption & thereby ↓OXYGEN DEMAND WITHOUT ALTERING HEMODYNAMICS
Indication	Used whenever needed as add-on therapy to nitrates, CCBs or b-blockers
ADRs	GIT disturbances
Contraindications	1-Hypersensitivity reaction 2-In pregnancy & lactation, because it is teratogenic.



2. Ranolazine

Pharmacological effect	**Inhibits the late sodium current,** which increases during ischemia and affects Na dependent-Ca Channels causing after-depolarization contraction
Precautions	1- It prolongs the QT interval so contraindicated with Class Ia & III antiarrhythmic drugs (which also prolong QT interval) 2- Toxicity develops due to interaction with CYT 450 inhibitors as; diltiazem, verapamil, ketoconazole, macrolide antibiotics, grapefruit juice
Indication	Ranolazine has antianginal as well as antiarrhythmic properties. It is indicated for the treatment of chronic angina and may be used alone or in combination with other traditional therapies. It is most often used in patients who have failed other antianginal therapies.

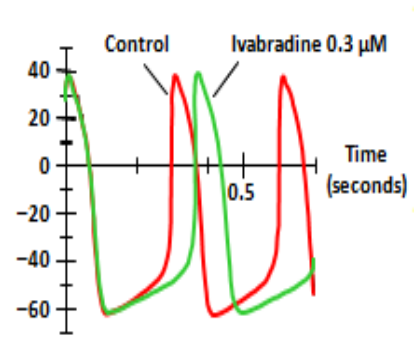


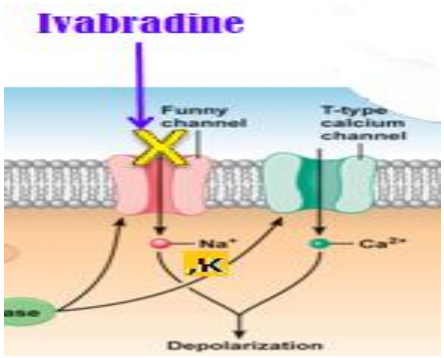
Ivabradine

6. Ivabradine

Selectively blocks I_f
(I_f current is an inward Na+/K+ current that activates pacemaker cells of the SA node)

Acts on the " Funny Channel" a special Na channel in SAN, reduces slope of depolarization → ↓HR → ↓myocardial work → ↓**Myocardial O_2 demand** (No effect on the force of contraction)
It has the same effects of B-blockers, so it could be used with patients who can't tolerate B-blockers





CONCOMITANT DISEASE	DRUGS COMMONLY USED IN TREATING ANGINA		
NONE	Long-acting nitrate	β-Blockers	Ca^{2+} channel blockers
RECENT MYOCARDIAL INFARCTION	Long-acting nitrate	β-Blockers	
ASTHMA, COPD	Long-acting nitrate		Ca^{2+} channel blockers
HYPERTENSION	Long-acting nitrate	β-Blockers	Ca^{2+} channel blockers
DIABETES	Long-acting nitrate		Ca^{2+} channel blockers
CHRONIC RENAL DISEASE	Long-acting nitrate	β-Blockers	Ca^{2+} channel blockers

KEY: Drug class — Commonly used drugs; Drug class — Less effective drugs

Helmi's case

Helmi, a 62-year-old male smoker with type 2 diabetes mellitus and hypertension presents with a 4-month history of exertional chest pain. Physical examination shows a blood pressure of 152/90 mm Hg but is otherwise unremarkable. The ECG is normal, and laboratory tests show a fasting blood glucose value of 110 mg/dL, glycosylated hemoglobin 6.0%, creatinine 1.1 mg/dL, total cholesterol 160, LDL 120, HDL 38, and triglycerides 147 mg/dL. He exercises for 8 minutes, experiences chest pain, and is found to have a 2-mm ST-segment depression at the end of exercise.

Q1:Which signs or symptoms of Helmi suggest diagnosis of angina pectoris?	Exercise induce, chest pain and depression of ST segment*. *sign of ischemia
Q2:What life style modifications should Helmi carry out?	Quit smoking, control of diabetes, diet control and moderate exercise.
Q3:What triggers the onset of symptom's in Helmi?	Exercise
Q4:What factors worsen the symptoms in case of Helmi?	Smoking, hypertension, diabetes and enhanced LDL.
Q5:What is the possible underlying cause of Helmi's exertional pain?	Atherosclerotic plaque
Q6:If Helmi was prescribed nitrates & tolerance developed to their effects, how to overcome tolerance to nitrates?	Nitrate tolerance can be overcome by: Smaller doses at increasing intervals (Nitrate free periods twice a day) & Giving drugs that maintain tissue SH group e.g. Captoril.
Q7:Which antianginal drug is the best choice for the case of Helmi? And Why?	Nitroglycerine, if became tolerant to nitrates choose Ca channel blockers or beta blockers.
Q8:If Helmi dose not respond to monotherapy, what other drug should be added to his regimen?	Ca channel blockers (selective to blood vessels e.g. **Amlodepine**) + beta blockers
Q9:Which antihyperlipidemic drug should be prescribed to Helmi?	Statins, to decrease LDL levels.

Antianginal drugs - summary

Drug/Class	HR	BP	Wall Tension	Contractility	O2 Supply
Beta-blockers	↓	↓	No effect /↑	↓	No effect
CCBs:					
Verap/Dilt	↓	↓	↓	↓	↑
Dihydropyridines	No effect/ reflex ↑	↓	↓	No effect	↑
Nitrates	No effect/ reflex ↑	No effect	↓	No effect/ reflex ↑	↑
Ranolazine	No effect	No effect	↓	No effect	No effect

Drugs	Stable angina	Variant angina	Unstable angina	Others
Beta Adrenoceptor Blockers	Cardio-selective are preferred. Prolong use reduces incidence of sudden death.	**Contraindicated** because they constrict the coronary artery	Halts progression to AMI, improves survival	IN AMI they reduce infarct size, reduce morbidity & mortality
Calcium channel blockers	Used for Prophylaxis	Relief the spasm and prevent attacks in variant angina	Rarely added in refractory cases	
Organic nitrates	Sublingual GTN to relief attack and for situational prophylaxis, Oral isosorbide mono/dinitrate for persistent prophylaxis	Sublingual GTN to relief pain	IV GTN	- IV GTN in AMI and refractory AHF - isosorbide mono/dinitrate+ hydralazine for CHF if ACEI is contraindicated
K channel openners e.g.Nicorandil	Prophylactic 2nd line therapy	Used in refractory variant angina		
Trimetazidine				Used as an add on therapy

Quiz

THANK YOU FOR CHECKING OUR WORK

THE PHARMACOLOGY TEAM

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